INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD
ISSN: 2455-0620 [Impact Factor: 6.719]
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value : 86.87
Volume - 8, Issue - 9, September - 2022 Publication Date: 30/09/2022

DOIs:10.2015/IJIRMF/202209049 --:-- Research Article

Synthesis of New N^3 - Substituted-1, 3, 4-Oxadiazol-2-yl Hydantoins as Active Antiepileptic Agents

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Abstract: *Ten different substituted hydantoin derivatives were prepared by condensation of different chloro-acetylated hetrocyclic moieties with alkali metal-cyanate in presence of quaternary ammonium salt. The reaction was found to proceed best in polar solvents. The compounds were screened for anticonvulsant activity, Di-phenyl hydantoin sodium was used as the reference drug.*
Three of the compounds showed significant anticonvulsant activity. Compound II, N^3 - (5-(p-dimethyl-amino-phenyl)-1, 3, 4,-oxadiazole-2 yl) hydantoin exhibited potent anticonvulsant activity.

Key words: *Antiepileptics, oxadiazole, phase-transfer catalyst. substituted hydantoins.*

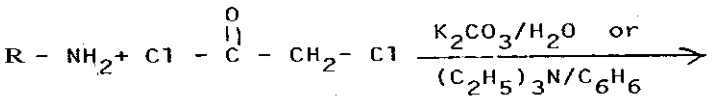
1. INTRODUCTION:

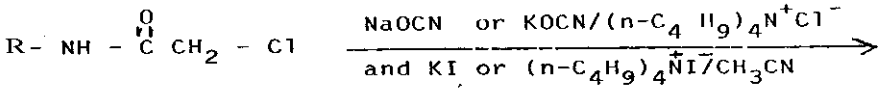
Antiepileptic specialists are utilized to diminish the number and seriousness of epileptic seizures. Various medications are viable in forestalling or decreasing the recurrence of seizures in around 80% of the epileptic patients. Several more di-substituted 1, 3, 4-oxadiazole derivatives have been synthesized and tested for their effective anti-epileptic activity (1-4). Frank et.al. (1926) (5) detailed the significance of N^3- substituted hydantoin as drugs with conceivable antiepileptic movement. The derivatives can be obtained by the substitution in the hydantoin ring at N^3 position (Orazi et.al.1974) (6). It was, in this way, thought worth-while to synthesize some new hydantoin derivatives with various heterocyclic moieties at N^3 position with the end goal of concentrating on their design-action relationship. The current correspondence manages the blend and anticonvulsant action of ten substituted hydantoins.

2. MATERIAL AND METHODS:

Synthesis

N^3-substituted hydantoin derivatives were synthesized by the method of Kim and Kwon (1982) (7) in two stages. First, chloro-acetylated heterocyclic mixtures were prepared by treating the heterocyclic compounds with chloro-acetyl chloride in dry benzene. In second stage, chloro-acetylated derivatives were treated with potassium cyanate in presence of catalytic amount of tetra-n-butyl-ammonium iodide as phase-transfer catalyst and potassium-iodide containing a polar solvent, acetonitrile. The general sequence of the chemical reaction may be depicted as follows:





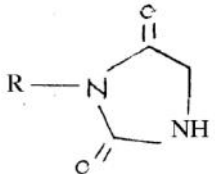
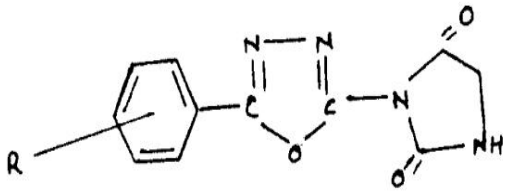


Table-1.The molecular formula, melting-point & percentage yield of substituted hydantoins of oxadiazole.



S. No.	R	X	Molecule formula	M.P °C	Yield %
I	5-phenyl-1,3,4-oxadiazole-2-yl	---	$C_{11}H_8N_4O_3$	242	70
II	5-phenyl-1,3,4-oxadiazole-2-yl	p-dimethylamino	$C_{14}H_8O_3N_5$	252	69.8
III	5-phenyl-1,3,4-oxadiazole-2-yl	p-methoxy	$C_{12}H_{10}N_4O_4$	235	72
IV	5-phenyl-1,3,4-oxadiazole-2-yl	p-ethoxy	$C_{12}H_{10}N_4O_4$	240	74
V	5-phenyl-1,3,4-oxadiazole-2-yl	p-hydroxy	$C_{11}H_8N_4O_4$	245	71
VI	5-phenyl-1,3,4-oxadiazole-2-yl	p-chloro	$C_{11}H_7O_3N_4Cl$	245	72
VII	5-phenyl-1,3,4-oxadiazole-2-yl	p-bromo	$C_{11}H_7O_3N_4Br$	241	70
VIII	5-phenyl-1,3,4-oxadiazole-2-yl	p-fluoro	$C_{11}H_7O_3N_4F$	262	64
IX	5-phenyl-1,3,4-oxadiazole-2-yl	o-chloro	$C_{11}H_7O_3N_4Cl$	240	69.8
X	5-phenyl-1,3,4-oxadiazole-2-yl	o-bromo	$C_{11}H_7O_3N_4Br$	234	67

The analysis of N, Cl, Br and F (found and calculated) did not differ more than 0.4%

3. ANTIEPILEPTIC ACTIVITY:

Male albino mice weighing 20-25 mg were used in the present study. They were maintained at an ambient temperature of 22 ± 1°C and had food and water ad.libitum. The mice were divided into groups of six animals each except otherwise mentioned. The test compounds were dissolved in polysorbate (Tween 80) and diluted with distilled water and were injected i.p.in a dose of 100 mg/kg to the mice. One group received standard drug, Diphenyl hydantoin sodium in a dose of 25 mg/kg i.p. The control group received vehicle only. The animals were observed for behavioral changes, if any, up to 1 hour of drug administration.

The anticonvulsant activity was studied by maximum electroshock seizures (MES). The electro-shock (48mA, 0.2 sec.) was delivered 1 hr. after the drug administration through a convulsiometer (Techno) by using ear electrodes according to the method of Swinyard et.al. (1952) (8). After the delivery of shocks, duration of various phases of MES (tonic flexion, tonic extensor and clonus) and of post seizure depression, defined as the time required to regain the righting-reflux (RR), was taken as the index for protection. The statistical significance of the difference in the mean values were calculated by the student's't' test.

Table-2. Effect of substituted hydantoins of oxadiazole on components of electroshock - induced seizures in male albino mice.

Compound No.	No. of Animals	Mean duration in seconds ± SEM			
		Flexor	Extensor	Clonus	Stupor
Vehicle Control	11	2.29 ± 0.16	15.09 ± 1.35	11.80 ± 3.19	53.80 ± 10.06
I	6	3.40 ± 0.50	0.00 ± 0.00****	5.00 ± 3.34	146.16 ± 34.11*

II	6	3.50 ± 0.23***	0.00 ± 0.00****	4.06 ± 0.96*	6.41 ± 1.11***
III	6	3.24 ± 0.21***	0.00 ± 0.00****	5.28 ± 3.36	7.91 ± 2.11*
IV	6	3.28 ± 0.24***	0.00 ± 0.00****	5.24 ± 3.21	7.94 ± 2.82*
V	6	3.42 ± 0.25***	1.71 ± 0.00****	4.09 ± 0.96*	12.42 ± 2.24***
VI	6	1.60 ± 0.06***	1.73 ± 1.22****	10.58 ± 1.86	13.70 ± 3.44***
VII	6	1.68 ± 0.08***	1.78 ± 1.28****	11.24 ± 1.88	14.72 ± 3.44***
VIII	6	1.72 ± 0.8***	1.84 ± 1.32****	11.28 ± 1.94	15.84 ± 4.22***
IX	6	1.60 ± 0.06***	1.72 ± 1.22****	7.72 ± 2.21	12.25 ± 3.12***
X	6	1.64 ± 0.08***	1.72 ± 1.22****	7.82 ± 2.24*	13.20 ± 3.18***
Diphenyl hydantoin sodium	6	1.63 ± 0.24*	0.00 ± 0.00****	2.20 ± 1.04****	4.73 ± 1.79***

P value in comparison to control group -*P: - < 0.05, **P :-< 0.025, ***P :-< 0.01, ****P: -< 0.001
'a' : Dose of 25 mg/kg i.p

4. RESULT:

Series of substituted hydantoin were synthesized and their structure, physical and chemical properties are summarized in Table 1.

The yield of the compounds varied from 64 to 74% with N^3-ethoxy-phenyl derivative having maximum yield. The yield of N^3–(5-p-ethoxyphenyl) 1, 3, 4- oxadiazole-2-yl hydantoin was also firmly high. Almost all the compounds showed high melting point ranging from 234 to 262°C. There was a marked variation in the result of anticonvulsant activity of N^3-substituted hydantoins (Table-2).

The compound I, II, III and IV offered significant anticonvulsant activity against electro-shock-induced seizures. However, compound VIII did not show any anticonvulsant activity. The compound I and II had maximum anticonvulsant activity on extensor component of electro-shock. However compound II had added advantage as it also decreased the duration of other components of electro-shock seizures, clonus to be specific.

Compound X had reduced significantly ($P < 0.05$) the clonic phase of electro-convulsion without affecting the tonic component.

There was a marked decreased in the value of flexor component of electro-convulsion in the compound VI, VII, IX and X.

The percent mortality rate was almost same in all the compounds as observed after 1 hour and 24 hours of chemo-shock induced seizures. The compound II offered lowest percent mortality rate in 50% of the animals with all the animals showing tremors depressant effect while compound II was found to be almost depressive

Compounds VII and VIII had marked irritant effect. Remaining compounds did not show any impropriate impact on the behavior of albino mice

Di-phenyl hydantoin sodium (25 mg/kg) afforded total protection against electro-shock induced seizures.

5. DISCUSSION:

The compounds having methoxy, ethoxy and di-methyl-amino substitution in their heterocyclic moiety in the hydantoin nucleus, in general, have shown good anticonvulsant activity. However, the compounds with ortho and para substitution of halogen atoms produced active (IX, X) as well as inactive (VIII) anticonvulsant compounds. Results indicate that almost all the hydantoins derivatives were active as compared to vehicle control as indicated by decreased duration of extensor component of electro-shock seizures.

Compound II with di-methylamino sodium substitution in hydantoin nucleus has significant huge anticonvulsant activity as indicated by decrease in extensor component, having an added advantage of lowest clonus duration as compared to compounds I, III and IV.

The substitution of chloro atoms at ortho and para positions of hydantoin derivatives does not show any significant effect on anticonvulsant activity of the compound. However, ortho substitution of chlorine atom had probably reduced the duration of clonus phase in compound IX as compare to para – substituted chlorine atom in compound VI.
Similarly, ortho substitution of bromine atom in compound X have reduced the duration of clonus phase as compared to para–substituted bromine atom in compound VII.

The fluoro - substituted derivatives of hydantoin was found to offer least anticonvulsant activity.
Compound I has also been found to possess CNS depressant effect. The depressant effect of this compound may probably be responsible for its anticonvulsant activity.

The order of anticonvulsant effect against electro-shock induced seizures was II > I > IV > VI
In conclusion it is suggested that substituted hydantoins with oxadiazole moiety are potent anticonvulsants and legitimate further analysis on different models of antiepileptic drug, screening of activity and toxicity.

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